Weight Loss by Low-Calorie Diet Versus Gastric Bypass Surgery in People With Diabetes Results in Divergent Brain Activation Patterns: A Functional MRI Study

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OBJECTIVE

Weight loss achieved with very-low-calorie diets (VLCDs) can produce remission of type 2 diabetes (T2D), but weight regain very often occurs with reintroduction of higher calorie intakes. In contrast, bariatric surgery produces clinically significant and durable weight loss, with diabetes remission that translates into reductions in mortality. We hypothesized that in patients living with obesity and prediabetes/T2D, longitudinal changes in brain activity in response to food cues as measured using functional MRI would explain this difference.

RESEARCH DESIGN AND METHODS

Sixteen participants underwent gastric bypass surgery, and 19 matched participants undertook a VLCD (meal replacement) for 4 weeks. Brain responses to food cues and resting-state functional connectivity were assessed with functional MRI pre- and postintervention and compared across groups.

RESULTS

We show that Roux-en-Y gastric bypass surgery (RYGB) results in three divergent brain responses compared with VLCD-induced weight loss: *1*) VLCD resulted in increased brain reward center food cue responsiveness, whereas in RYGB, this was reduced; *2*) VLCD resulted in higher neural activation of cognitive control regions in response to food cues associated with exercising increased cognitive restraint over eating, whereas RYGB did not; and *3*) a homeostatic appetitive system (centered on the hypothalamus) is better engaged following RYGB-induced weight loss than VLCD.

CONCLUSIONS

Taken together, these findings point to divergent brain responses to different methods of weight loss in patients with diabetes, which may explain weight regain after a short-term VLCD in contrast to enduring weight loss after RYGB.

Obesity and type 2 diabetes (T2D) are among the greatest global health challenges of our time (1,2). Health systems are heavily investing in population-based weight

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loss strategies, with ongoing debate about the most effective way to achieve long-term improvements in health. Weight loss achieved with very-low-calorie diets (VLCDs) can produce remission of T2D, lasting up to 2 years in motivated participants (3). However, at the population level, lifestyle interventions to achieve long-term weight loss are not widely successful, with some suggestion that severe calorie restriction induces hormonal and metabolic responses that encourage high rates of weight regain (4,5). Only bariatric surgery has been shown to produce enduring weight loss that translates into long-lasting amelioration and even remission of diabetes (6) and risk reduction for cardiovascular and cancer-related mortality (7). The mechanisms by which bariatric surgery produces its metabolic benefits remain incompletely understood (8), but changes in food preference and hunger after the surgery have been frequently reported and are likely to play a role (9). Functional MRI (fMRI) offers the opportunity to investigate the neural pathways that underpin different methods of weight loss.

A number of studies have reported changes in brain activation patterns before and after bariatric surgery (10–12), but few have focused on participants with diabetes and prediabetes (13), and none have longitudinally investigated the evolution of these patterns in participants with obesity and diabetes who lose weight through diet versus surgery. Furthermore, reductions in insulin levels or hyperglycemia may confound observed differences in fMRI signal in longitudinal studies of people with diabetes who have lost weight, highlighting the need for a study in which groups of people with diabetes, matched for improvements in glycemia by different interventions, are compared and contrasted.

To address these important clinical questions, we compared two groups of participants with prediabetes or noninsulin-requiring T2D using fMRI before and after weight loss achieved by Roux-en-Y gastric bypass surgery (RYGB) or VLCD. We hypothesized that there would be differences in brain activation patterns in patients undergoing RYGB versus VLCD. Drawing on previous literature, we identified divergent longitudinal changes in brain activity that fall into three themes. Theme 1 centers on the hypothesis that RYGB induces a reduction in brain reward center food cue responsiveness not seen with calorie restriction alone. Theme 2 is centered on whether neural activation in regions associated with cognitive control or "rational" decision making differs with dieting compared with surgery in people with diabetes. Theme 3 focuses on whether a homeostatic system (centered on the hypothalamus) is differentially engaged following RYGB-induced weight loss than VLCD.

RESEARCH DESIGN AND METHODS

Recruitment

Participants were recruited at the National Institute for Health Research (NIHR) Imperial Clinical Research Facility at Hammersmith Hospital, London, U.K., from July 2016 to October 2018 (ClinicalTrials.gov identifier NCT01945840) (14). All participants gave written consent, and the study was performed in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the U.K. National Health Service (NHS) Health Research Authority West London Research Ethics Committee (reference number 13/LO/1510). Volunteers for the VLCD group were recruited from clinics at the Imperial Weight Centre (IWC) or from newspaper advertising, whereas patients already listed for surgery at the IWC were recruited to the RYGB group. Key eligibility criteria were male or female participants aged between 18 and 70 years who met NHS criteria for bariatric surgery and with a diagnosis of prediabetes (impaired fasting glucose, impaired glucose tolerance, or HbA_{1c} of 6.0–6.4% [42–47 mmol/mol]) or T2D according to World Health Organization criteria. Accepted participants had a stable HbA_{1c} of $<$9.0% (75 mmol/mol) controlled by either diet or a single oral hypoglycemic agent. Key exclusion criteria were any comorbidities or medications that could compromise the validity and safety aspects of the study, a current history of smoking or substance misuse, pregnancy, and a history of eating disorders.

Study Visits

Preintervention (visit 1), the RYGB participants underwent an fMRI scan in the morning after having fasted since 10:00 P.M. the night before and completed the Dutch Eating Behavior Questionnaire (DEBQ) (15). RYGB was performed laparoscopically according to standardized techniques by three designated surgeons at IWC. An identical fMRI scan and study visit were repeated at postoperative week 4 (visit 2). VLCD participants attended the research unit at visit 1 before starting a complete meal replacement VLCD of 800 kcal/day for 4 weeks (Cambridge Weight Plan, Corby, U.K.). An fMRI scan was performed at visit 1 and at visit 2 at week 4 (Supplementary Fig. 1*A*). At arrival, before, and after the MRI scan and then before and after lunch, participants completed a 100-mm visual analog scale (VAS) that rated nausea and pleasantness to eat. At each visit, fasting blood samples for gut hormones were collected in lithium heparin tubes containing aprotinin (Nordic Pharma, Reading, U.K.) and a dipeptidyl peptidase 4 inhibitor, Diprotin A (20 μg/mL blood; Enzo Life Sciences, Exeter, U.K.). Samples were placed on ice and centrifuged at 4°C within 10 min of collection, and separated plasma was stored at −80°C until analysis. Active glucagon-like peptide 1 (GLP-1), ghrelin, and glucose-dependent insulinotropic polypeptide levels were measured by a customized MILLIPLEX magnetic bead-based multianalyte metabolic panel immunoassay (Millipore, Rockville, MD). Total peptide YY (PYY) was measured by an in-house radioimmunoassay using a polyclonal antiserum recognizing both $PYY_{1–36}$ and $PYY_{3–36}$ (16). The intra- and interassay coefficient of variation was $<$10% and $<$15%, respectively, for the MILLIPLEX metabolic panel and $<$10% for the radioimmunoassay. The lowest limit of detection was 0.8 pmol/L for GLP-1, 4.1 pmol/L for ghrelin, 0.3 pmol/L for glucose-dependent insulinotropic polypeptide, and 8.7 pmol/L for PYY.

fMRI

Pre- and postintervention MRI sessions lasted ∼60 min and in addition to a localizer and a high-resolution T1-weighted anatomical image, included food images task and resting state scans.

Food Images Task

This was a block design task that was presented in two separate runs and consisted of food (appetizing and bland) and object images derived from the study of Beaver et al. (17). For the purposes of the current study, the images were grouped into two

categories: food images (divided into low- and high-calorie types) and nonfood objects (see exemplar images in Supplementary Fig. 1*B*). Each block included five images, and each image was presented for ~3s. The blocks were presented in a pseudorandom order and were mixed with equally long resting blocks showing a blank screen. Each run consisted of 40 blocks (10 of each category), and the images in each run differed.

Resting State

During the resting-state scan, participants were asked to keep their eyes open and to fixate on a white cross in the middle of a gray screen.

MRI Acquisition

Scanning was performed on a Siemens Verio 3T MRI scanner with a 32-channel phased array head coil. Anatomical images were acquired at the beginning of each scan using a T1-weighted magnetization-prepared rapid acquisition with gradient echo pulse sequence (1-mm isotropic voxels, repetition time = 2,300 ms, echo time = 2.98 ms, flip angle = 9°, 160 axial slices). Functional images were acquired using a 3D echo planar imaging sequence (3-mm isotropic voxels, repetition time = 2,000 ms, echo time = 30 ms, flip angle = 80°, 35 axial slices). A different number of volumes was acquired for each task depending on the task duration: Each food image task was ~10 min and 305 volumes, and the resting state was ~8 min and 240 volumes.

Whole-Brain Analysis

Imaging data were processed using FSL version 5.0.4 (https://www.fmrib.ox.ac.uk/fsl/) (Oxford Centre for Functional Resonance Imaging of the Brain [FMRIB]). Anatomical images were skull stripped and segmented using the anatomical processing script fsl_anat in FSL. Functional image series were preprocessed using the following parameters: high-pass filter (100 s), head motion correction, and 6-mm (full width at half maximum, Gaussian) spatial smoothing. The functional images of each individual were then coregistered to their T1 structural image and a standard anatomical template in the Montreal Neuroscience Institute (MNI) 152 space. For the analysis of the food images and fMRI battery task, a standard general linear model was used, as implemented in the FEAT module in FSL (18) and incorporated FMRIB's Improved Linear Model (FILM) correction for autocorrelation. In the first-level models, regressors derived from the onset times of each stimulus condition were convolved with a γ-function to simulate the hemodynamic response function, and the first temporal derivatives of each stimuli time series were included in the model. Additionally, regressors derived from head motion parameters were included as regressors of no interest. First, a group-level analysis used a mixed-effects model (FMRIB's Local Analysis of Mixed Effects [FLAME-1]) and a statistical threshold of Z = 2.3 ($P < 0.05$ cluster corrected for multiple comparisons). Second, a follow-up group-level analysis was performed on a subgroup of participants tightly matched for weight (n = 7 per intervention) using a fixed-effects model and a statistical threshold of Z = 2.3 ($P < 0.05$ cluster corrected for multiple comparisons). Contrasts were computed to model the effect of each stimulus against baseline and the effects among the different stimuli in each task. For the food images task, the contrasts were food or objects greater than baseline and food greater than objects.

For the region of interest (ROI) analysis, we specified a combination of functional and anatomical ROIs depending on the particular hypotheses tested and the most appropriate and practical methods for defining regions in different areas. Most of our ROIs were functionally defined since many areas that are described as relevant to food cue responsivity, such as the dorsolateral prefrontal cortex (dlPFC), are not accurately defined as distinct anatomical areas in the brain and may either encompass two or more anatomical regions or be a subpart of a larger anatomical region. In addition, functional definitions are often considered superior to anatomical with regard to intersubject variability (19,20). To avoid biases, all the functional ROIs for the food task were independently defined on the basis of the group mean effect of the task in all participants in the contrast all stimuli great than baseline. This means that all scans from all participants were grouped to look for clusters of brain activity that were activated in response to seeing pictures (of any variety, food and nonfood) compared with baseline (resting periods where no pictures were shown). These brain areas were visually compared with an established map (the Harvard-Oxford atlas) of specified regions (21). This procedure is in line with the recommendations of Friston et al. (22), who suggested that this method of functional ROI definition is preferable to procedures using a separate localizer experiment. ROIs in this constrained functional space that corresponded to the five areas that made up our reward system and the five areas that comprised the executive control system were created, and their coordinates (in MNI space) are listed in Supplementary Table 1.

For the hypothalamus, a functional definition was not possible because of its small size and location in an area with high magnetic susceptibility effects. Therefore, an anatomical definition was used following the localization procedure described in Baroncini et al. (23). The same mask was used as a seed in the resting-state network analysis. The primary purpose for incorporating the hypothalamus in this analysis was to test the hypothesis that interconnectedness between homeostatic and hedonic networks in the brain might be modulated differentially by different means of weight loss.

Data from ROIs were extracted for each scan. Food cue–induced signal (above baseline) was compared for each participant (postintervention − baseline) and each ROI. Differences between intervention groups was compared using two-tailed unpaired Student t tests after testing for Gaussian distribution using a D'Agostino-Pearson test.

Resting-State Analysis

A seed-based connectivity analysis was performed on the resting-state data using the anatomical hypothalamus ROI as a mask, as previously applied (24–26). Time series were extracted from the hypothalamus seed for each participant and included as regressors in the first-level model. Additionally, each participant's anatomical images were segmented into white matter and cerebrospinal fluid masks, and time series were extracted for each (using FSL's fsl_anat and FMRIB's Linear Image Registration Tool [FAST] modules). These time series were included in the models as regressors of no interest along with standard head motion regressors, and the model also incorporated

FILM correction for autocorrelation. Subsequently, a higher-level analysis compared baseline and postintervention scans using FSL's FEAT module and a mixed-effects cluster-corrected ($Z > 2.3$, $P < 0.05$) FLAME-1 model.

Statistical Analyses

A power calculation, using the SD of the reward system ROI data set from previous fMRI studies in our unit comparing reward network activation in the fed versus the fasted state, estimated that 16 participants per group were required to establish a visit 2 – visit 1 mean percent blood-oxygen-level–dependent (% BOLD) signal difference between RYGB and VLCD of 0.1 with a power of 0.8 and an α of 0.05 (18). Continuous data for other measurements between the VLCD and RYGB groups are presented as mean ± SEM following testing for Gaussian distribution with the D'Agostino-Pearson test. Fisher exact tests were used to compare categorical variables and differences between proportions. Paired *t* tests were used to determine changes in clinical measurements between baseline and postintervention unpaired between groups. VAS scores over the course of the study visits were adjusted for baseline and compared by repeated-measures nonparametric Friedman test with Dunn multiple comparison post hoc test. Changes in DEBQ scores pre- and postintervention in each group were compared using Mann-Whitney tests. Linear regression was performed to assess the relationship between longitudinal changes in MRI signal per ROI and changes in gut hormone levels or questionnaire score. A threshold of $P < 0.05$ was used for statistical significance. Statistical analysis was performed using GraphPad Prism 8 software (GraphPad Software, La Jolla, CA).

RESULTS

A total of 16 participants in the RYGB group and 19 in the VLCD group completed pre- and postintervention study visits and were included in the analysis. Preintervention, participants were matched for age and sex, with a similar spread of diabetes diagnoses and use of oral antidiabetic drugs (Table 1). The RYGB group at baseline weighed, on average, 119.9 ± 6.1 kg and lost 12.3 ± 0.89 kg (−10.4%), whereas the VLCD group started, on average, at 109.2 ± 4.98 kg and lost 8.4 ± 0.56 kg (−8.4%) by visit 2 at 4 weeks ($P = 0.002$ for absolute weight loss between groups at 4 weeks). At 12 months, the VLCD group regained all the weight previously lost, while the RYGB group continued to lose weight. HbA_{1c} values between visit 1 and visit 2 fell to a similar degree in each group (53.9 ± 2.65 mmol/mol to 46.0 ± 1.97 for the RYGB group and 53.1 ± 2.52 to 46.6 ± 2.1 for the VLCD group). Importantly, there was also a comparable reduction at 4 weeks in both fasting glucose (−2.48 ± 0.44 for RYGB vs. −1.84 ± 0.50 mmol/L for VLCD, $P = 0.35$) and fasting insulin (−7.13 ± 1.82 for RYGB vs. −6.81 ± 1.15 mIU/L for VLCD, $P = 0.88$) following the interventions. A subgroup of very closely matched patients for weight loss ($n = 7$ weight-matched from each intervention, weight loss 8.2 ± 0.68 kg for the RYGB subgroup and 8.2 ± 0.67 kg for the VLCD subgroup) was also identified for subgroup analyses that were free of the potential confounding effects of unmatched weight loss (Supplementary Table 2).

There was a significant increase in fMRI activity in both groups when participants looked at images of food compared with nonfood objects, confirming the validity of the task design. Group-level (FLAME-1) analysis did not reveal a between-group and between-treatment difference. Fixed-effects group-level analysis on the weight-matched subgroups ($n = 7$) confirmed that brain areas

Table 1—Baseline clinical and biochemical characteristics of participants in the study

	RYGB	VLCD	*P* value
Participants, *n*	16	19	
Sex			0.17
Female	13	11	
Male	3	8	
Age (years)	48.6 ± 14.4	46.2 ± 10.8	0.57
Weight (kg)			
Visit 1	119.9 ± 6.1	109.2 ± 4.98	0.18
Visit 2	107.7 ± 5.98	100.8 ± 4.54	0.35
Weight loss between fMRI scans			
Visit 2 − visit 1 (kg)	−12.3 ± 0.89	−8.42 ± 0.66	0.002
%	−10.42 ± 0.86	−7.66 ± 0.39	0.004
Follow-up weight 1 year after study entry (kg)	83.80 ± 4.43	109.06 ± 7.15	0.0064
HbA_{1c} (mmol/mol)			
Visit 1	53.94 ± 2.65	53.11 ± 2.52	0.82
Visit 2	46.00 ± 1.97	46.63 ± 2.1	0.83
Fasting glucose (mmol/L)			
Visit 1	8.37 ± 0.46	7.64 ± 0.60	0.37
Visit 2	5.89 ± 0.25	5.83 ± 0.25	0.85
Change	−2.48 ± 0.44	−1.84 ± 0.50	0.35
Fasting insulin (mIU/L)			
Visit 1	19.52 ± 1.73	16.23 ± 1.38	0.14
Visit 2	12.38 ± 1.40	9.43 ± 0.84	0.07
Change	−7.13 ± 1.82	−6.81 ± 1.15	0.88
Treatment for diabetes during the study, *n*			>0.99
Diet	8	10	
Metformin	7	9	
Dipeptidyl peptidase 4 inhibitor	1	0	

Data are mean ± SEM unless otherwise indicated. Sixteen patients with impaired glucose tolerance or noninsulin-requiring T2D were treated with RYGB, and 19 patients were treated with VLCD for 4 weeks. An fMRI scan was performed at baseline (visit 1) and again after the intervention (visit 2). For most patients, visit 2 occurred at 4 weeks after study entry, except for three patients in the RYGB group who had a scan at 12 weeks postoperatively because of medical or logistical reasons. Demographic and clinical characteristics for both study groups at baseline (visit 1) and at the end of the intervention (visit 2) are shown. *P* values represent the results of unpaired *t* tests between the RYGB- and VLCD-treated groups.

involved in both hedonic responses and executive control were significantly deactivated in the RYGB group postintervention compared with the VLCD group (Supplementary Fig. 2*D*). These concepts are expanded in the a priori ROI analysis below. Of note, comparison of visit 1 food cue responses showed no differences between the groups (Supplementary Fig. 2*A*). VAS scores revealed no differences between the VLCD group and the RYGB group both pre- and postintervention in terms of nausea ratings or prospective scores for pleasantness to eat on the study visit days (Supplementary Fig. 2*B* and *C*).

Functional ROIs Related to the Reward System

Functional ROIs pertaining to the hedonic reward/salience network in feeding studies (amygdala, caudate, insula, nucleus accumbens, orbitofrontal cortex [OFC], putamen) were analyzed, chosen because of their functional implications in other similar studies (10,27). All the reward system regions of interest tended toward a relative hyporesponsiveness to food cues postintervention in the RYGB group compared with the VLCD group (Fig. 1*A*, no *P* values reached < 0.05). In the subgroup analysis of seven highly matched participants for weight loss, the divergent pattern of activation in the VLCD group versus deactivation in the RYGB group held true significantly for the nucleus accumbens ($P = 0.001$) and the putamen ($P = 0.004$) (Supplementary Fig. 2*E*). Overall, the complete VLCD group demonstrated a relative augmentation in responsivity to food cues within the combined reward system ROIs postintervention ($P = 0.03$) (Fig. 1*B*). This finding was in keeping with the whole-brain analysis of that group as well as evident in the weight-matched subgroup comparison ($P = 0.01$) (Supplementary Fig. 2*F*). A correlation analysis of changes in gut hormone levels between visits and changes in reward ROI activity did not reveal any strong associations (Supplementary Table 3).

The DEBQ looks at three elements of disordered eating: restraint, emotional eating, and susceptibility to external food cues. Eight participants in the VLCD group and five in the RYGB group did not fill out or return their second questionnaire, so baseline data sets for these individuals were excluded. The reduction in external cue score (which best reflects how a person is enticed by food cues) from baseline to postintervention was significantly greater for the RYGB group compared with the VLCD group ($P = 0.01$) (Fig. 1*C*). Taken together, these findings suggest that RYGB-mediated weight loss results in a brain activation pattern that underpins a reduced reward drive to food cues.

Functional ROIs Related to the Executive Control System

When we compared postintervention to preintervention (visit 2 – visit 1) in each group, we saw no significant difference in whole-brain activation in response to food cues in the RYGB group, whereas in the VLCD group, we saw significantly increased brain activation in the posterior cingulate gyrus, inferior frontal gyrus, and middle temporal gyrus. These are all areas with a role in executive control that have previously been shown to be modulated with weight loss (28,29) and suggest that weight loss with VLCD requires a stronger executive (inhibitory/restraint) response to food images compared with RYGB, implying that patients may need to engage a greater restraint or effort to suppress food cravings following VLCD than RYGB. Using functional ROIs that are based on the NeuroSynth guide to the regions involved in executive control/decision making (30), we defined functional ROIs that grouped into our executive control system. As for the reward system analysis, no single ROI was significantly more engaged in one treatment group than the other postintervention (Fig. 1*D*); however, taken as a whole, the executive control system was significantly deactivated postintervention in the RYGB group compared with the VLCD group ($P = 0.017$) (Fig. 1*E*).

The restraint subsection of the DEBQ is most likely to reflect the participants' ability to exert executive control on their eating. Interestingly, both the RYGB and the VLCD groups reported higher restraint scores after their weight loss intervention, although this only reached significance compared with baseline in the RYGB group (Fig. 1*C*). A correlation matrix of DEBQ score and ROI signal changes by group revealed, allowing for multiple comparisons, that longitudinal changes in food cue responsivity in the paracingulate gyrus correlated with DEBQ restraint score increases in the VLCD group but not the RYGB group (Fig. 2*A* and *B*). The signal change in the paracingulate gyrus ROI did diverge in the two groups but not significantly so (mean visit 2 − visit 1 signal change −12.2 vs. 0.3 in the paracingulate gyrus in the RYGB group vs. the VLCD group, respectively, $P = 0.08$). Caudate signal similarly diverged between the two groups (Fig. 1*A*), but again, only in the VLCD group did this longitudinal signal change correlate with changes in DEBQ restraint scores (VLCD: $R^2 = 0.78$, $P = 0.007$; RYGB: $R^2 = -0.41$, $P = 0.21$) (Fig. 2*C* and *D*). Taken together, these results suggest that there appears to be a reduced requirement to activate the executive control system following RYGB compared with VLCD. While both groups reported greater restraint scores on the questionnaire, the neural substrates underpinning this may be different.

Homeostatic Versus Nonhomeostatic Systems

An anatomically defined ROI for the hypothalamus also revealed a divergent pattern in hypothalamic signal change pre- and posttreatment between the two intervention groups. The task-based signal change in the hypothalamus between visit 1 and visit 2 decreased in the RYGB group, whereas it increased in the VLCD group ($P = 0.046$). Hypothalamic signal change pre- and postintervention was significantly correlated with the achieved weight loss for the RYGB group but not the VLCD group (Fig. 2*E* and *F*). When the hypothalamus was used as a seed region in resting-state analysis, we found an increased postsurgical resting-state connectivity between the hypothalamus and numerous brain areas, including the dlPFC, putamen, globus pallidus, and cingulate gyrus, whereas this connectivity increase was absent in the VLCD group after weight loss (Fig. 2*G*). Taken together, these findings suggest that RYGB engages a stronger homeostatic regulation of food intake than VLCD.

CONCLUSIONS

This study is the first to report on these three interconnecting phenomena occurring in people with diabetes in a longitudinal comparison between weight loss groups. The importance of such longitudinal trial designs in weight loss settings has been highlighted by others (31). The complex appetitive brain processes that control

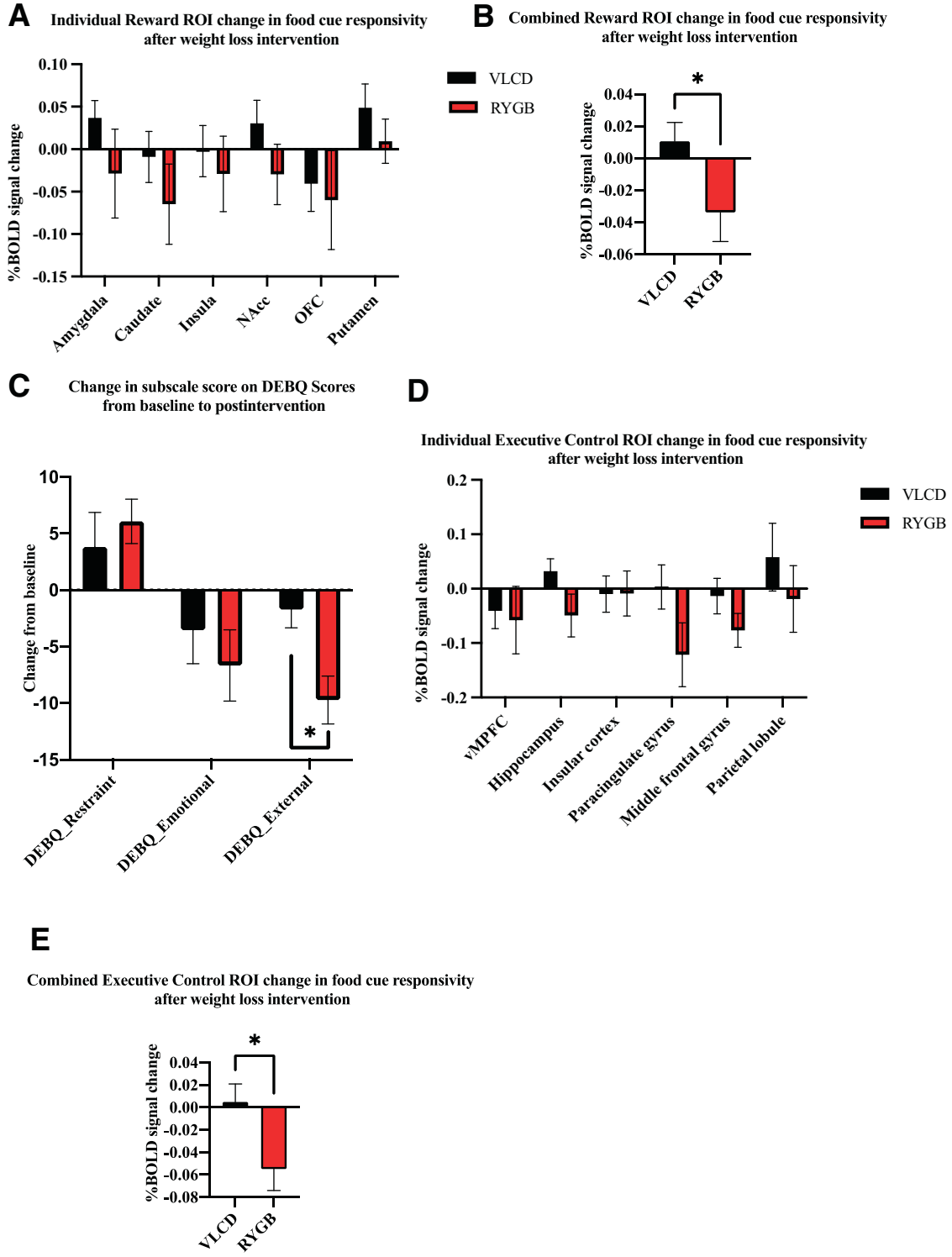

Figure 1—Functional ROI analysis of food task. *A*: Mean % BOLD signal change in a priori (functional) reward-based ROIs in response to food images against objects in the VLCD and RYGB groups. Mean % BOLD signal change (postintervention vs. baseline) across all six ROIs (amygdala, caudate, insula, nucleus accumbens [NAcc], OFC, putamen—the reward system) in response to food images in the VLCD and RYGB groups. Data are mean ± SEM (VLCD n = 19, RYGB n = 16). For comparison of the ROIs, amygdala P = 0.23, caudate P = 0.31, insula P = 0.61, NAcc P = 0.18, OFC P = 0.76, and putamen P = 0.32. *B*: Taking the reward system as a whole (summed ROIs described in *A*), there was a significant downactivation in the RYGB group in response to food cues after surgery compared with the pre- to postchange in the VLCD group. *C*: Changes in the restraint subsections of the DEBQ scores before and after weight loss in either group. Using a one-sample Wilcoxon test, only the scores for DEBQ restraint and DEBQ external in the RYGB group (not the VLCD group) changed significantly post- vs. preintervention (P = 0.008 and P = 0.0008, respectively). Between-group comparison (visit 2 – visit 1 for RYGB vs. VLCD) showed a significant divergence only on the DEBQ restraint scores (P = 0.01). *D*: Mean % BOLD signal change in a priori (functional) executive control ROIs in response to food images against objects in the VLCD and RYGB groups. Mean % BOLD signal change (postintervention vs. baseline) across all six ROIs (ventromedial prefrontal cortex [vMPFC], hippocampus, insular cortex, paracingulate gyrus, middle frontal gyrus, parietal lobule—the executive control system) in response to food images in the VLCD and RYGB groups. Data are mean ± SEM (VLCD n = 19, RYGB n = 16). For comparison of the ROIs, vMPFC P = 0.80, hippocampus P = 0.07, insular cortex P = 0.99, paracingulate gyrus P = 0.08, middle frontal gyrus P = 0.18, and parietal lobule P = 0.39. *E*: Taking the executive control system as a whole (summed ROIs described in *D*), there was a significant downactivation in the RYGB group in response to food cues after surgery compared with the pre- to postchange in the VLCD group. *$P < 0.05$.

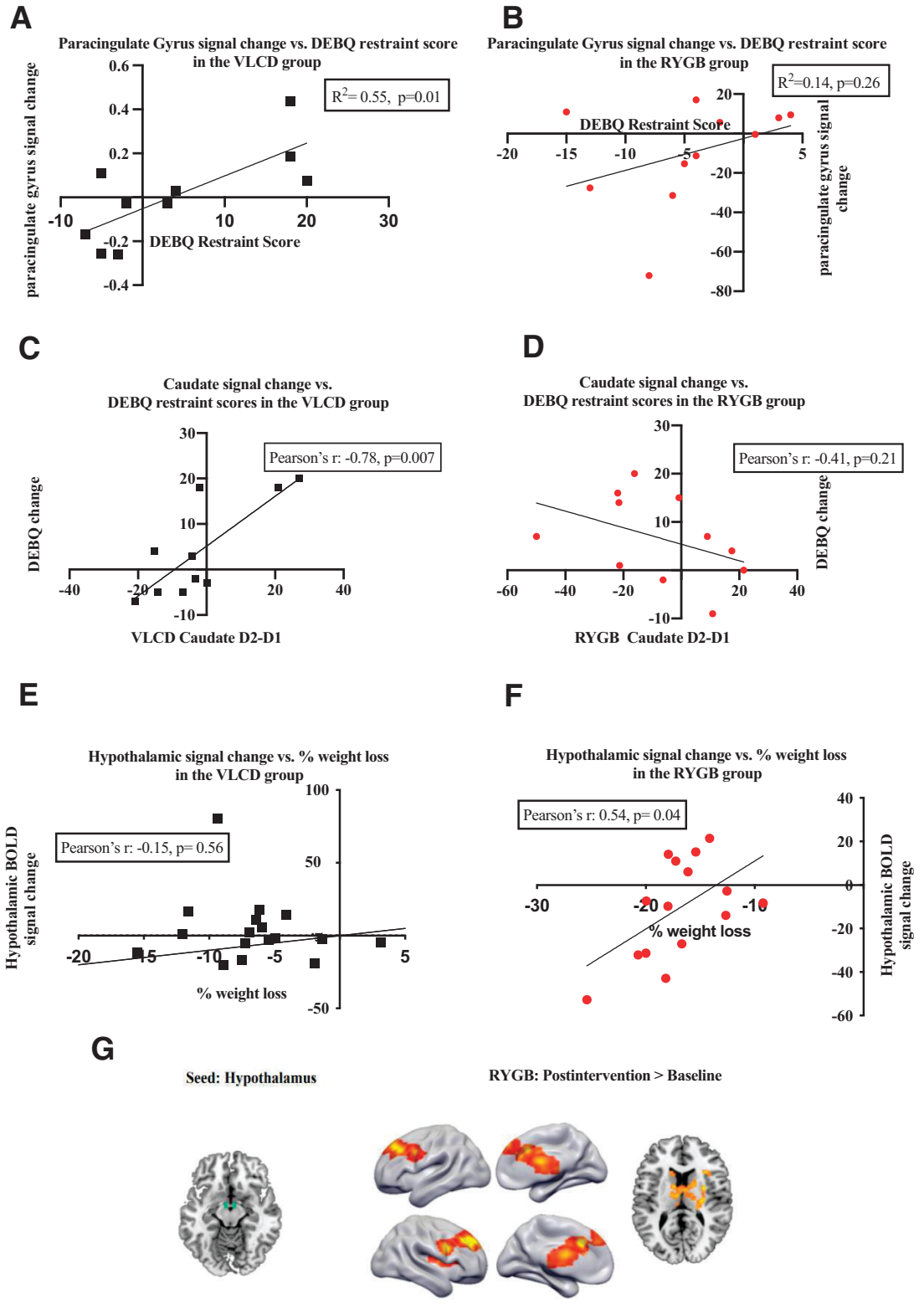

Figure 2—Brain region correlates with DEBQ and weight loss and resting-state data. *A–D*: Paracingulate gyrus and caudate signal change from pre- to postintervention strongly correlated with DEBQ restraint scores in the VLCD group but not in the RYGB group (matched fMRI and DEBQ data sets were available for n = 11 per group). *E* and *F*: Hypothalamic signal (anatomical ROI) decreased in response to food cues in the RYGB group, whereas it increased in the VLCD group (P = 0.05). Of note, body weight loss correlated with signal change in the hypothalamus only in the RYGB group. *G*: On resting-state analysis, the hypothalamus was used as a seed region. Seed-based connectivity analysis revealed a significantly augmented connectivity between the hypothalamus and numerous areas, including the putamen, globus pallidus, and the cingulate gyrus postsurgery, whereas this connectivity increase was absent in the VLCD group after weight loss.

food intake have been described as three interconnecting networks: cognitive, hedonic, and homeostatic (32). We show that RYGB results in three divergent brain responses compared with VLCD-induced weight loss. First, RYGB induces a relative reduction in food cue responsiveness in areas of the brain known to be associated with food reward processing. Second, weight loss with RYGB is facilitated by a reduced requirement for higher neural activation of cognitive control regions, which is linked to cognitive restraint over eating as measured by the DEBQ. Third, a homeostatic appetitive system centered on the hypothalamus is better engaged following RYGB-induced weight loss than VLCD, with reduced activation in response to food cues in the hypothalamus and increased connectivity to reward areas in the RYGB group at rest, suggesting that reduced hunger may mediate the observed changes in food reward after RYGB. The findings suggest that RYGB induces multiple brain activation patterns that may guard against weight regain, whereas VLCD induces changes that may make continued weight loss more difficult to sustain. Because we studied our participants at an early stage postoperatively, we cannot rule out that other changes in brain activity may become apparent at later stages. It should also be noted that while the groups were not randomized to their intervention, there was no obvious difference in their baseline characteristics. We are not able to provide data for brain responses to a return to a eucaloric diet in patients who had lost weight. Both groups lost >10% of their body weight by the second scan; however, the RYGB group lost significantly more than the VLCD group, although there is no evidence to suggest that the results presented here are not due to the different mechanisms of weight loss as opposed to any baseline or total body weight loss differences between the comparator groups. We have also presented subjective questionnaire scores during the scan visits to exclude the possibility that the surgical group was experiencing more nausea or other noxious sensations (as a result of the recent surgery) than the VLCD group.

The first theme in our study is that RYGB induces a reduction in brain reward center food cue responsiveness compared with calorie restriction alone. The phenomenon of reward hyporeactivity after surgical weight loss is well established in the fMRI literature, although these studies did not include people with diabetes. Ochner et al. (12) reported a reduction in post-RYGB activation to high-fat food cues in a range of corticolimbic areas within the mesolimbic reward pathway, including the ventral striatum and putamen, and Faulconbridge et al. (11) reported a significant decline in ventral tegmental area response to food images after RYGB but not in weight-stable control subjects. We have previously shown that within a hedonic reward system (OFC, amygdala, anterior insula, nucleus accumbens, and caudate), the fMRI signal in response to high-calorie food cues was lower in patients who had undergone RYGB than weight-matched control subjects and in patients who have undergone RYGB compared with gastric band surgery (10). Of particular note, we found in the current study that caudate activity correlated strongly with restraint scores in the VLCD group, who also exhibited significantly less improvement in external cue DEBQ scores postintervention compared with the RYGB group. These findings point to the possibility that patients in the VLCD group were more susceptible to food cravings. Indeed, Volkow et al. (33) demonstrated increased dopamine levels in the caudate nucleus of hungry subjects exposed to food cues, and Small et al. (34) conversely reported a decrease in dopaminergic binding potential in the dorsal striatum of fasted subjects who have been allowed to eat to satiety. An fMRI study by Pelchat et al. (35) designed to elicit food cravings in hungry subjects confirmed significant caudate activation in this setting.

The concept that weight loss might be related to activity in regions implicated in cognitive control seems intuitive to anyone who has tried, and failed, to diet. In 2008, Rosenbaum et al. (28) reported that maintenance of a reduced body weight was associated with increased neural activity in systems mediating aspects of executive and decision-making functions (middle temporal gyrus, inferior frontal gyrus, and lingual gyrus). In line with this, Kahathuduwa et al. (36) investigated the effects of a 3-week hypocaloric total meal replacement diet compared with an isocaloric typical diet (portion control) and reported that meal replacement increased activation in the anterior cingulate and primary motor and left insular cortices, areas involved in executive inhibitory control over ingestion and food reward. Neseliler et al. (37) tested the hypothesis that weight loss would be related to activity in regions implicated in cognitive control. They showed increased fMRI signals in the same regions associated with cognitive control as depicted in our results, which correlated with weight loss at 1 month. Conversely, Zoon et al. (38) reported that the post-RYGB shift in food preferences away from high-calorie foods correlates with decreased superior parietal activation to food cues. However, in the closest comparable study to ours, Baboumian et al. (39) compared whole-brain activation in response to food cues after RYGB with a control group that lost weight with diet alone and reported that the surgery group showed increased dlPFC activation in response to appetizing food cues, suggesting greater cognitive dietary inhibition. This differs from our findings, but it is important to note that the dietary weight loss group in this study was no longer on caloric restriction at the time of the second scan, which may have removed the metabolic drive for enhanced cognitive restraint. dlPFC activation is believed to be instrumental in weight loss (40), and it may seem counterintuitive that a reduced activity in areas of cognitive control would protect against weight regain. However, our data suggest that there is a reduction in requirement for cognitive control after RYGB, which may be driven by the reduction in reward appeal to food cues and an improved connectivity with the homeostatic system. In our surgical group, this seemed to be driven largely by changes in the paracingulate gyrus, an area well described to be involved in cognitive response inhibition (41).

The homeostatic regulation of body weight control is centered on the hypothalamus, which is able to assimilate hormonal cues from adipose tissue and the gut to modulate appetite (42). Here, we propose that this homeostatic system is better engaged following RYGB-induced weight loss than VLCD. It has been previously reported that hypothalamic activation in response to food cues is more pronounced after surgery as a marker of enhanced satiation (38). It has been reported that in healthy, normal weight volunteers, hypothalamic fMRI signal positively covaries with circulating PYY levels (43). Both PYY and GLP-1 levels are elevated in the postprandial state following bariatric surgery (44), while fasting ghrelin levels have

been shown to decline postoperatively (45). ten Kulve et al. (46) reported that the GLP-1 analog exenatide promotes hypothalamic activity in humans and hypothalamic connectivity with the rest of the brain, and Meyer-Gerspach et al. (47) extended this to the action of endogenous GLP-1, revealing that administration of the GLP-1 receptor antagonist exendin(9-39) disrupted functional connectivity between homeostatic (hypothalamus) and reward-related (OFC) brain regions. More recently, another study by ten Kulve et al. (48) showed that in 10 obese females undergoing RYGB, activation was reduced in the caudate nucleus in response to food and that this was interrupted after RYGB with GLP-1R blockade. Circulating levels of ghrelin have also been implicated in modulating activation of the reward system. Changes in fasting ghrelin levels post-RYGB have been positively linked with changes in BOLD activation in the ventral tegmental area, a key area for reward processing (11), while similar associations were also found with other reward-related areas (dlPFCs) in obesity (49). We did not see any correlation between this increase in hypothalamic connectivity or reward hypoactivity with prevailing gut hormone levels in our patient groups, suggesting that the changes in brain activity that we have detected are not simply explained by acute changes in gut hormone secretion but may represent a longer-term response. We find that the hypothalamus becomes significantly more connected to higher brain centers following bariatric surgery, suggesting the engagement of a homeostatic appetitive system that feasibly promotes maintenance of satiety. The hedonic drive may therefore be decreased by the hypothalamic drive in a bottom-up fashion, since a reduced subconscious hunger drive feeds into reduced cravings and a drive to eat high-calorie foods (50).

In summary, this is the first longitudinal fMRI study to compare groups of people with diabetes who have lost weight through either RYGB or VLCD. We provide evidence that those who have undergone bariatric surgery experience three complementary changes in appetitive brain processing compared with those who have lost weight through calorie restriction. These divergent brain responses to different methods of weight loss may explain why there is a tendency to regain weight after completion of a short-term VLCD. Any effective and durable weight loss program aimed at inducing remission of T2D through weight loss should perhaps focus on interventions that induce changes in brain activity similar to those induced by RYGB, and our findings point the way toward fMRI-based methods for assessing the likely long-term efficacy of such interventions.

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